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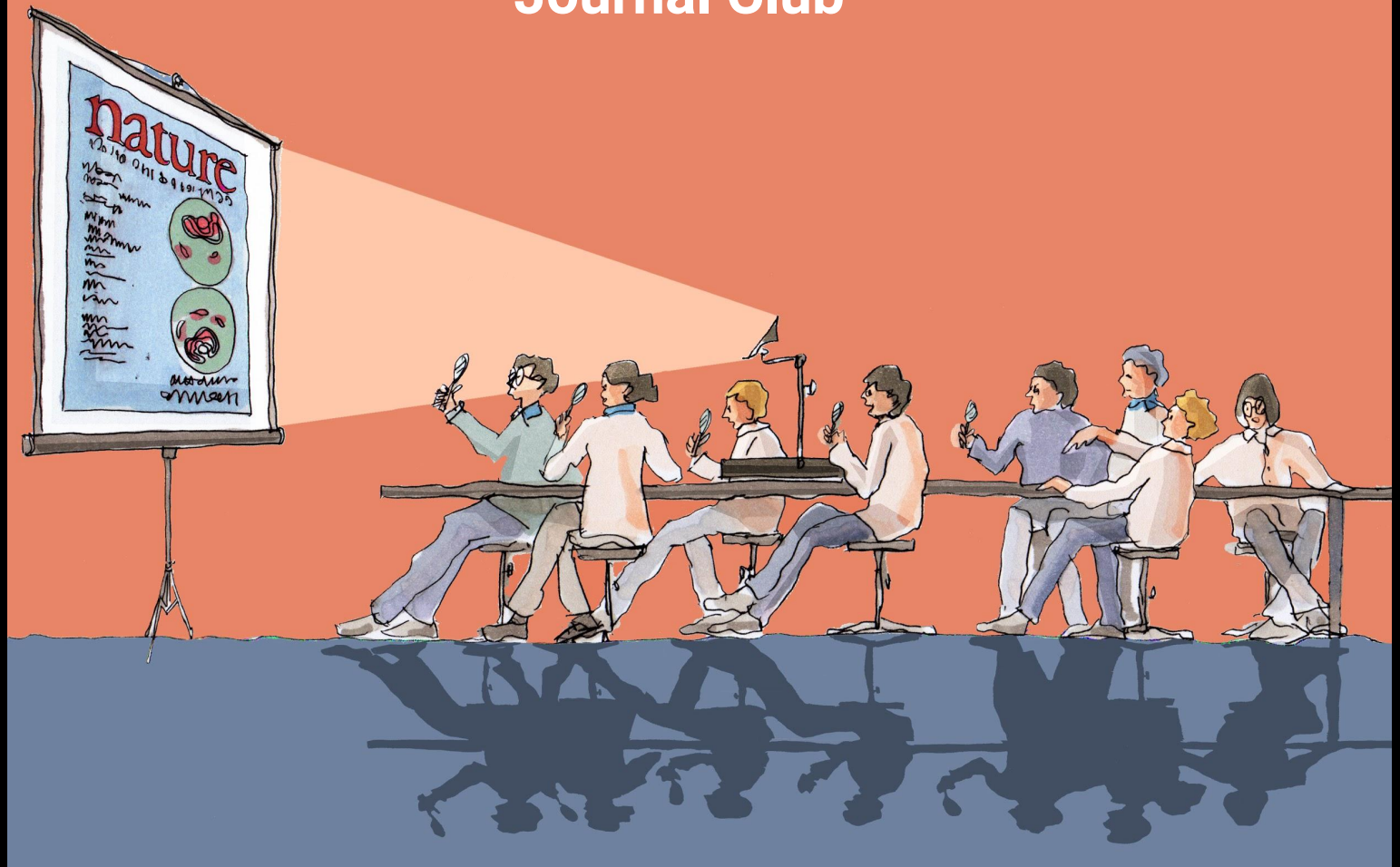
Brandon Stell
The PubPeer Foundation

Journal Club



The Scientific Record

The basis for:

Current and future research
(including clinical trials)

Public policy
(medical, environmental, etc)

Healthcare

Johannes Kepler 1627

The Scientific Record

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Healthcare

Forbes / Pharma & Healthcare

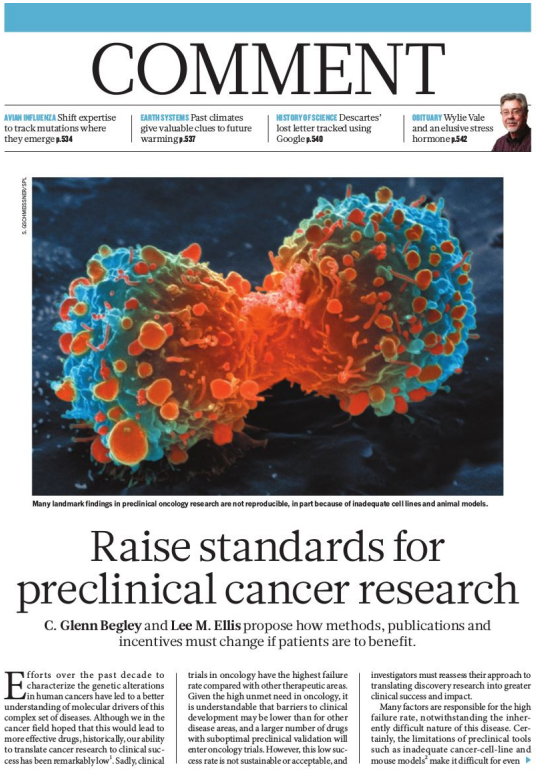
JAN 15, 2014 @ 12:37 PM 45,237 VIEWS

Medicine Or Mass Murder? Guideline Based on Discredited Research May Have Caused 800,000 Deaths In Europe Over The Last 5 Years

"...European Society of Cardiology guideline recommending the liberal use of beta-blockers [...] was partly based on unreliable research."

“Fifty-three papers were deemed ‘landmark’ studies [...] scientific findings were confirmed in only 6 (11%) cases.”

-Amgen USA



COMMENT

AVIAN INFLUENZA Shift expertise to track mutations where they emerge p.314 | EARTH SYSTEMS Past climates give valuable clues to future warming p.337 | HISTORY OF SCIENCE Descartes' lost letter tracked using Google p.548 | OBITUARY Wylie Vale and an elusive stress hormone p.542

S. GSCHMEISSNER/SPL

Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.

Raise standards for preclinical cancer research

C. Glenn Begley and **Lee M. Ellis** propose how methods, publications and incentives must change if patients are to benefit.

Efforts over the past decade to characterize the genetic alterations in human cancers have led to a better understanding of molecular drivers of this complex set of diseases. Although we in the cancer field hoped that this would lead to more effective drugs, historically, our ability to translate cancer research to clinical success has been remarkably low[1]. Sadly, clinical trials in oncology have the highest failure rate compared with other therapeutic areas. Given the high unmet need in oncology, it is understandable that barriers to clinical development may be lower than for other disease areas, and a larger number of drugs with suboptimal preclinical validation will enter oncology trials. However, this low success rate is not sustainable or acceptable, and investigators must reassess their approach to translating discovery research into greater clinical success and impact.

Many factors are responsible for the high failure rate, notwithstanding the inherently difficult nature of this disease. Certainly, the limitations of preclinical tools such as inadequate cancer-cell-line and mouse models[2] make it difficult for even ▶

29 MARCH 2012 | VOL 483 | NATURE | 531

Nature 2012

In 67 projects only 33% of published preclinical studies could be validated to the point at which projects could continue.

-Bayer HealthCare Germany

CORRESPONDENCE

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

Nature Rev Drug Discovery 2011

“100 experimental and correlational studies published in three psychology journals.

39% of effects were subjectively rated to have replicated the original result”

Open Science Framework

RESEARCH ARTICLE SUMMARY

PSYCHOLOGY

Estimating the reproducibility of psychological science

Open Science Collaboration*

Science 2015

“...the complex system for ensuring the reproducibility of biomedical research is failing and is in need of restructuring.”

NATURE | COMMENT

Policy: NIH plans to enhance reproducibility

Francis S. Collins & **Lawrence A. Tabak**

27 January 2014

Francis S. Collins and Lawrence A. Tabak discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

Nature 2014

Pressure to Publish

“best” journals = career success
(e.g. jobs, funding, promotions, etc.)

Potentially “high-impact” research at expense of careful work

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CRISPR

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Journal Club on the Record

CRISPR-Cas9 Knockin Mice for Genome Editing and Cancer Modeling
Cell, 2014
Randall J Platt, Sidi Chen, Yang Zhou, Michael J Yim, Lukasz Swiech, Hannah R Kempton, James E Dahlman, Oren Parnas, Thomas M Eisenhaure, Marko Jovanovic, Daniel B Graham, Siddharth Jhunjhunwala, Matthias Heidenreich, Ramnik J Xavier, Robert Langer, Daniel G Anderson, Nir Hacohen, Aviv Regev, Guoping Feng, Phillip A Sharp, Feng Zhang
17 comment(s)

CASFISH: CRISPR/Cas9-mediated in situ labeling of genomic loci in fixed cells
Proc. Natl. Acad. Sci. U.S.A., 2015
Wulan Deng, Xinghua Shi, Robert Tjian, Timothée Lionnet, Robert H Singer
10 comment(s)

Genome-wide CRISPR Screen in a Mouse Model of Tumor Growth and Metastasis
Cell, 2015
Sidi Chen, Neville E. Sanjana, Kaijie Zheng, Ophir Shalem, Kyungheon Lee, Xi Shi, David A. Scott, Jun Song, Jen Q. Pan, Ralph Weissleder, Hakho Lee, Feng Zhang, Phillip A. Sharp
5 comment(s)

crispr

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Comments (17):

1

Unregistered Submission: (November 12th, 2014 4:26pm UTC)

Very nice paper. Congrats. Quick question: in Figure 3D, the CTR lane on the blot is, according to the legend, extracts derived from mice injected with AAV1/2-sgLacZ. If this vector is a non-specific sgRNA control (ie schematized in 3B but with sequence directed against lacZ rather than NeuN), should these mice not also be expressing Cre, and also Cas9 by virtue of the Cre activity?

Reply Report

Permalink

1

Unregistered Submission: (November 16th, 2014 8:42pm UTC) Author

Thank you for your great question. The legend for this figure (Figure 3) reads: "(D) Representative immunoblot of brain tissue dissected from Cre-dependent Cas9 mice injected with either AAV1/2-sgNeuN or AAV1/2-sgLacZ or not injected, showing NeuN depletion only in NeuN-targeted mice.

External links

Popular press (5)

- CRISPR Knock-in Mouse Debuts
- Researchers engineer 'Cas9' animal models to study disease and inform drug discovery
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Moderated:

- Based on publicly verifiable information
- No *ad hominem* arguments
- Comments evaluated entirely on their content

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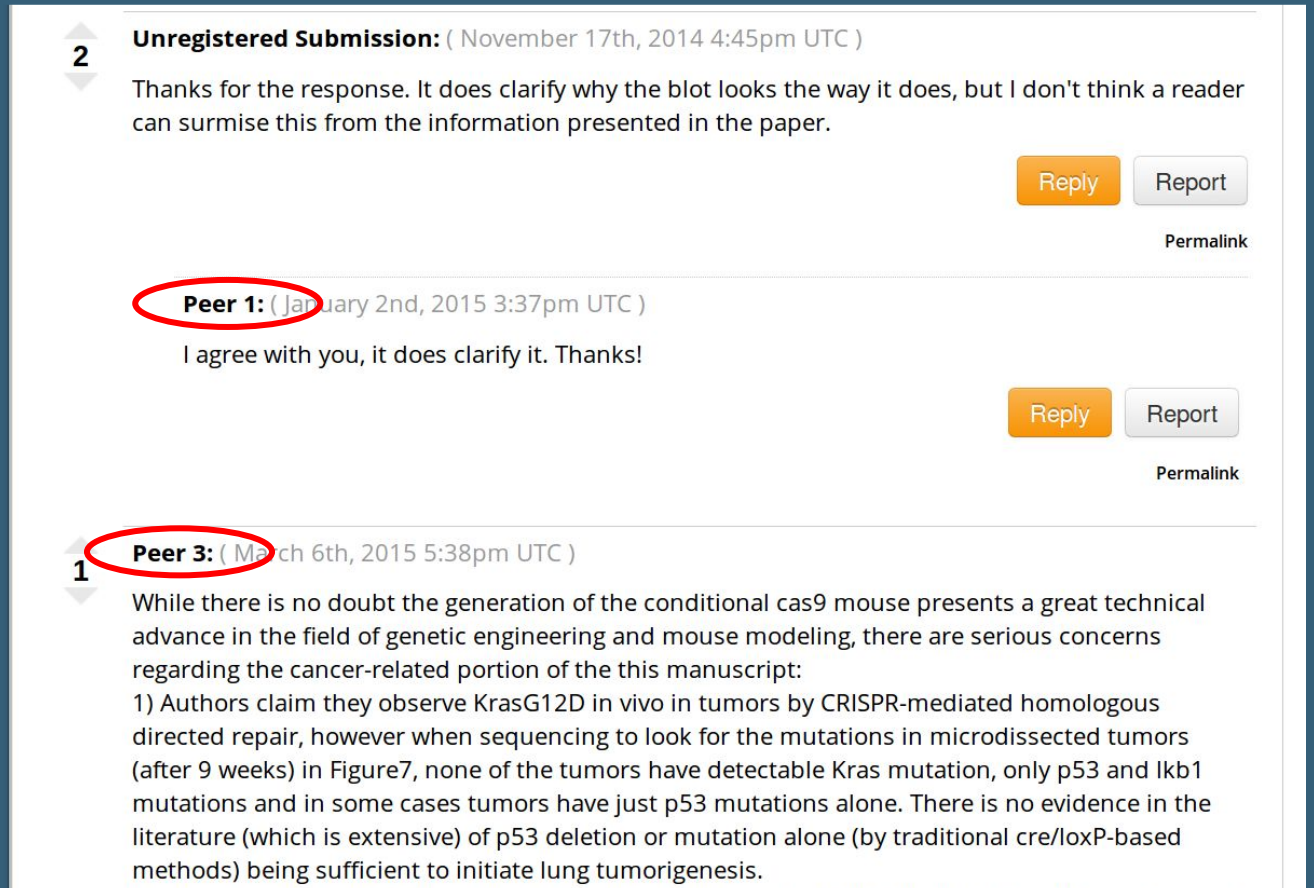

2

Unregistered Submission: (November 17th, 2014 4:45pm UTC)

Thanks for the response. It does clarify why the blot looks the way it does, but I don't think a reader can surmise this from the information presented in the paper.

Reply Report

Permalink

Peer 1: (January 2nd, 2015 3:37pm UTC)

I agree with you, it does clarify it. Thanks!

Reply Report

Permalink

1

Peer 3: (March 6th, 2015 5:38pm UTC)

While there is no doubt the generation of the conditional cas9 mouse presents a great technical advance in the field of genetic engineering and mouse modeling, there are serious concerns regarding the cancer-related portion of the this manuscript:
1) Authors claim they observe KrasG12D in vivo in tumors by CRISPR-mediated homologous directed repair, however when sequencing to look for the mutations in microdissected tumors (after 9 weeks) in Figure7, none of the tumors have detectable Kras mutation, only p53 and lkb1 mutations and in some cases tumors have just p53 mutations alone. There is no evidence in the literature (which is extensive) of p53 deletion or mutation alone (by traditional cre/loxP-based methods) being sufficient to initiate lung tumorigenesis.

Accounts:

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- “Peer” consistent within threads

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Cell

Volume 159, Issue 2, 9 October 2014, Pages 440–455

Resource

CRISPR-Cas9 Knockin Mice for Genome Editing and Cancer Modeling

Randall J. Platt[1, 2, 3, 4, 14], Sidi Chen[5, 6, 14], Yang Zhou[2, 3], Michael J. Yim[1, 2, 3, 4], Lukasz Swiech[1, 2, 3, 4], Hannah R. Kempton[1, 2, 4], James E. Dahlman[5, 7, 8], Oren Parnas[1], Thomas M. Eisenhaure[1, 11], Marko Jovanovic[1], Daniel B. Graham[1], Siddharth Jhunjhunwala[5], Matthias Heidenreich[1, 2, 3, 4], Ramnik J. Xavier[1], Robert Langer[5, 7, 8, 9], Daniel G. Anderson[5, 7, 8, 9], Nir Hacohen[1, 10, 11], Aviv Regev[1, 6, 12], Guoping Feng[1, 2, 3, 13], Phillip A. Sharp[5, 6], , , Feng Zhang[1, 2, 3, 4, 13], ,

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doi:10.1016/j.cell.2014.09.014

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Highlights

- Generation of mouse lines with Cre-dependent and constitutive Cas9 expression
- Viral/nonviral delivery of sgRNA to the brain, vasculature, immune cells, and lung

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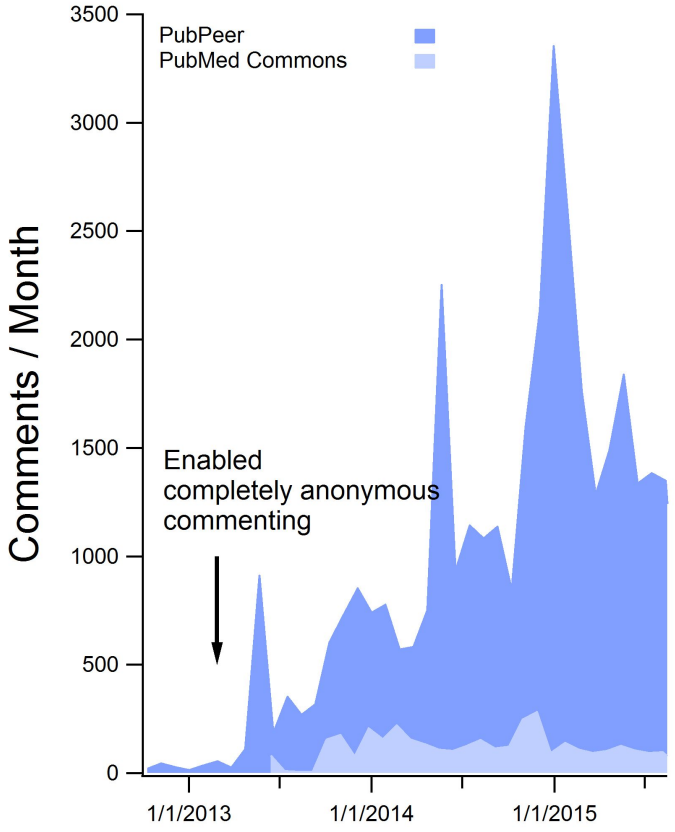

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- Put focus on the data
- Encourage wider use of preprints (arXiv, bioRxiv)

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